BANTAO Journal 2022; 20(2): 58-64

BJ

BANTAO Journal

Original article

Anti-Cytomegalovirus Hyperimmune Immunoglobulins as Adjunctive Therapy during Acute COVID-19 in Kidney Transplant Recipients: A Single-Center Retrospective Cohort Study

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Abstract

Introduction. Anti-CMV immunoglobulin (CMV-HIG) contains antibodies against various infective pathogens and not only against the cytomegalovirus (CMV), thus possibly mimicking the convalescent plasma.
Methods. A retrospective analysis concerning the practice of CMV-HIG off-label use during acute COVID-19 in kidney transplant recipients (KTR).
Results. From March 2020 to August 2022, 403 KTR (59.8% male) who developed COVID-19 were eligible for investigation. 151(44.4%) patients required hospitalization, and eighteen (5,6%) mechanical ventilation. Thirty-four (8.4%) patients received CMVHIG. Two patients had CMV reactivation and received CMVHIG 2 ml/kg in five doses. Others had hypogammaglobulinemia which was an additional off-label indication for using CMVHIG during acute COVID-19. 22 patients (6.5%) died, 4 of them from the CMVHIG group.
Conclusion. A correction of hypogammaglobulinemia, potential remodeling of the immunological response, and CMV reactivation during acute infection, may justify the use of CMVHIG during acute COVID-19.

Keywords: COVID-19, SARS-CoV-2, CMV, Hyperimmune anti-CMV globulin

Introduction

The pandemic of the coronavirus disease 2019 (COVID-19) has resulted in more than 690 million infections and almost 7 million deaths by July 2023 [1]. Advanced age, obesity, hypertension, diabetes, immunosuppression, and other chronic diseases have all been associated with increased severity of COVID-19 [2-4]. However, almost 50% of severe cases occur without obvious pre-existing conditions [4]. Cytomegalovirus (CMV) is a widely prevalent herpes virus. CMV-induced immune system remodeling was suggested in the pathogenesis of SARS-CoV-2 infection, and may be associated with more severe COVID-19 forms [5,6].
Treatment of acute COVID-19 remains challenging, while even vaccination failed to protect immunocompromised patients due to frequent breakthrough infections [7]. COVID-19 convalescent plasma (CP) contains neutralizing SARS-CoV-2 antibodies obtained from patients who recovered from acute COVID-19 but has been used with inconsistent results [8,9]. However, it had an important role in the early era of COVID-19 treatment when neither effective vaccines nor monoclonal antibodies were available on the market. Although the role of CP remains controversial, it may remain an important tool for the treatment of immunocompromised patients [10]. Intravenous immunoglobulins (IVIG) are widely used as additional treatment for patients with severe COVID-19 due to their immunomodulatory actions which can be potentially useful [11-14]. Hyperimmune anti-CMV immunoglobulin (CMV-HIG) has been approved as an adjuvant treatment for patients with CMV infection]15]. The product contains antibodies against various infective pathogens and not only against the CMV [16], thus possibly mimicking the convalescent plasma. At the beginning of the COVID-19 pandemic, with no available treatment or vaccine, we were the first to hypothesize that CMV-HIG might provide passive protection against SARS-CoV-2 [17].
Herein, we report our experience in off-label treatment of kidney transplant recipients with CMVIG in the context of SARS-CoV-2 infection.

Material and methods

This retrospective observational study comprised kidney transplant recipients with acute SARS-CoV-2 infection who received off-label CMV-HIG during acute SARS-CoV-2 infection. Treatment was individually chosen according to the attending transplant nephrologist.

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It was based on patients' history, severity of acute COVID-19 and laboratory findings (hypogammaglobulinemia, positive CMV DNA). The study was approved by the Ethics Committee with the informed consent from the patients.

Primary outcomes of the study were indications for the use of CMV-HIG (prevention or therapy of CMV infection), CMV-HIG protocol and dosages. Secondary outcomes included outcome of treatment, percentage of patients who reactivate CMV, adverse events, rehospitalizations after acute COVID-19, and follow-up results from the start of treatment until 6 months after the end of treatment with CMVHIG.

To assess clinical complications, patients were interviewed by a standardized survey by trained transplant nephrologists to recount symptoms during the acute illness and whether they persisted or some new occurred to assess clinical complications. Patients also underwent a detailed physical examination. Additional diagnostic methods were used individually (laboratory, radiologic). Data on immunosuppressive regimen and acute COVID-19 characteristics were recorded. Venous blood samples were collected for complete blood count, biochemistry, coagulation examinations (prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen), D-dimers, C3, C4, total complement, platelet aggregation with ADP (adenosine 5′-diphosphate), serum electrophoresis, donor-specific antibodies, and virology (molecular diagnostic detection for cytomegalovirus (CMV), Epstein-Barr virus (EBV) and BK virus (BKV)). Donor specific antibodies were determined by Luminex bead-based technology (One lambda). Results were compared with historical values. We had no data regarding the SARS-CoV-2 serology.

Patients have been in continuous follow-up, with reassessment at six months after acute SARS-CoV-2 infection.

Categorical data were presented by absolute and relative frequencies. The normality of the distribution of continuous variables was tested by the Shapiro-Wilk test. Continuous data were described by the median and the limits of the interquartile range (IQR). The Mann-Whitney U test was used to compare the median between two groups, while Fisher's exact test was used to analyze the differences between proportions. Logistic regression analysis was used to analyze the independent factors associated with the development of clinical complications or laboratory abnormalities. A stepwise multivariable logistic regression was used to assess the association between potential risk factors and development of laboratory or clinical complications, adjusting for known confounders. Variables assessed included demographic characteristics (ie, age, gender, primary kidney disease), clinical characteristics (ie, different comorbidities), acute COVID-19 characteristics (ie, presentation, need for hospitalization). Parameters with statistical significance in the univariate analysis were incorporated into the multivariate logistic regression model for in-depth analysis. The level of significance was set at an Alpha of 0.05. Considering the relatively small sample size and the possibility of overfitting in the multivariate logistic regression model, we adopted a forward stepwise method (probability for stepwise: entry $P<0.05$, removal $P>0.1$) for logistic regression analysis to reduce the number of independent variables entering the model. There was no substitution of the missing data. The statistical analysis was performed using MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www. medcalc.org; 2020) and the IBM SPSS Stat. 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

From March 2020 to August 2022, 403 patients (59.8 % male) who received renal allograft at our institution developed COVID-19 and were eligible for investigation. The most common primary kidney diseases were glomerulonephritis (28%) and autosomal dominant polycystic kidney disease (15.3%).

Patients' characteristics are presented in Table 1. Hospitalization during acute SARS-CoV-2 infection was necessary for 151(44,4%) patients. Eighteen (5,6%) patients required mechanical ventilation. Thirty-four (8.4%) patients received CMVHIG during acute COVID-19. Eleven patients (33%) from the CMVHIG group and forty-six (20%) from the non-CMVHIG group received at least one dose of vaccine before developing acute

Table 1. Patients' characteristics. TX, transplantation; BMI, body mass index; No, number, CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; IQR, interquartile range

	Median (IQR)			P*
	CMVHIG	Other	Total	
Age (years)	52.5(45-66.5)	57(46-64.75)	57(46-65)	0.57
TX vintage (months)	85.5(59-138.75)	96.5(53-138)	95.5(53-137.75)	0.88
BMI (kg/m^2)	25.14(23.4-28.48)	26.6(23.98-29.37)	26.5(23.92-29.32)	0.17
No of AHT drugs	3(1-4)	2(1-3)	2(1-4)	0.04
Steroid dose	5(5-7.5)	5(5-5)	5(5-5)	0.11
CKD-EPI eGFR	42.5 (32-53.5)	49(35-63)	48(35-62)	0.13
Proteinuria	0.32 (0.17-0.91)	0.23(0.12-0.49)	0.23(0.13-0.51)	0.03
*Mann Whitney U test				

COVID-19.
Patients who received CMVHIG more frequently had diabetes (38.3% vs.22.6%, p=0,04), a history of CMV infection after the transplantation (24.2% vs. 10.1%, p=0.01), needed more antihypertensive drugs and more frequently had a history of acute rejection (26.5 vs. 13.1 %, p=0.03).
During acute COVID-19, patients treated with CMVHIG more frequently had pneumonia that required hospitalization and mechanical ventilation (Table 2).

Table 2. Clinical presentation during acute COVID-19 in patients treated with CMVHIG and patients wo did not receive CMVHIG. Other symptoms included chest pain, abdominal pain, and loss of smell and taste

Acute COVID	Number (%) patients			P*
	CMVHIG	Other	Total	
Febrility	29(85.3)	252(80.3)	281(80.7)	0.48
Diarrhoea	9(26.5)	46(14.7)	55(15.9)	0.08
Respiratory	27(79.4)	226(72.7)	253(73.3)	0.40
No symptoms	1(3)	24(7.8)	25(7.3)	0.49†
Pneumonia	30(90.9)	135(45)	165(49.5)	<0.001
Other symptoms	15(44.1)	61(16.5)	76(18.9)	<0.001
Hospitalization	31(93.9)	120(39.1)	151(44.4)	<0.001
Mechanical ventilation	5(17.9)	13(4.4)	18(5.6)	0.01†

*χ^2 test;†Fisher exact test

Treatment during acute SARS-CoV-2 infection included immunosuppression modification in 261 patients (64.7%) (Table 3), remdesivir (61 patients (52,1%)), hydroxychloroquine (12 patients (2.9%), prophylactic use of low-molecular-weight heparin, glucocorticoids and antibiotics. Additionally, besides the patients who were treated with CMVHIG (34 patients, 8.4%), 17 patients (5.5%) received intravenous immunoglobulins, and four (1%) received convalescent plasma. Four patients (1%) were treated with tocilizumab. Other patients did not receive specific treatment because they either had a mild disease or did not inform us timely about the infection.

Table 3. Immunosuppressive therapy modification during acute COVID-19

	Number (%) of patients			P*
	CMVHIG	Other	Total	
MMF/Aza cessation	26(78.8)	122(41,8)	148(45.5)	<0.001
Decreased MMF/Aza	7(21.9)	106(36,3)	113(34.9)	0.12
Tac/CyA cessation	4(12.9)	1(0.3)	5(1.6)	<0.001
Decrease Tac/Cya	0	26(9)	26(8.9)	>0.99

*Fisher exact test"

Two patients had positive CMV DNA during acute COVID-19. Besides the ganciclovir, they both received CMVHIG 2 ml/kg in five doses. Hypogammaglobulinemia was an additional off-label indication for using CMVHIG during acute COVID-19. Hyperimmune anti-CMV globulin was applied in the dose of 1 ml/kg in 1 to 3 doses depending on the condition of patients, but also on the length of hospitalization.
Twenty-two patients (6.5%) died during acute COVID-19 (18 from multiorgan failure, three from myocardial infarction, and one from resistant CMV infection). Four of them were from the CMVHIG group.
Patients who survived acute COVID-19 underwent post-COVID-19 follow-up at the ambulatory visit 6-8 weeks after the infection. CMV reactivation was recorded in 21.7% of patients after recovery from acute COVID-19, with no statistically significant difference between patients who received CMVHIG during acute COVID-19 (30.4%) and patients who did not receive CMVHIG (20.7%). There were no significant differences in post-COVID complications between groups (Table 4).

Table 4. Post-COVID complications in patients treated with CMVHIG and patients who did not receive CMVHIG during acute COVID-19. CMV, cytomegalovirus; EBV, Epstein Barr virus; BKV, BK virus.

	Number (%) of patients			P*
	CMVHIG	Other	Total	
Kidney biopsy	4(16.7)	12(5.2)	16(6.3)	0.05
Neuropathy	0	10(4.3)	10(3.9)	0.61
CMV	7(30.4)	45(20.7)	52(21.7)	0.29
BKV	6(27.3)	54(25)	60(25.2)	0.80
EBV	12(54.5)	77(35.8)	89(37.6)	0.11
Hypogammaglobulinemia	10(45.5)	62(30.7)	72(32.1)	0.31

*Fisher exact test

Table 5. Post-COVID-19 laboratory analysis. CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; APTT, activated partial thromboplastin time

	Median (IQR)			P*
	CMVHIG	Other	Total	
Proteinuria	0.25(0.13-1.1)	0.26(0.14-0.59)	0.26(0.13-0.59)	0.70
CKD-EPI eGFR	44(28-58)	50 (35,25 - 69)	49 (35 - 69)	0.15
D-dimers	1.31(0.55-1.96)	0.56(0.34-1.06)	0.57(0.35-1.26)	0.01
Prothrombin time	1.17(1.08-1.27)	1.13(1.02-1.23)	1.13(1.04-1.24)	0.31
APTT	21.75(20.08-23.7)	22.2(20.8-23.4)	22.2(20.8-23.4)	0.52
Fibrinogen	4.6(3.3-6,45)	3.4 (2.93-4.4)	3.5(3-4.55)	0.01
Plattelet aggregation	71(62-78.5)	78(72-85)	78(72-84)	0.004
C3	1.21(0.99-1.46)	1.23(1.06-1.47)	1.22(1.06-1.46)	0.63
C4	0.30(0.23-0.36)	0.26(0.21-0.33)	0.26(0.21-0.33)	0.19
CH50	105(94-122)	105.5(94-113)	105(94-114)	0.51
*Mann Whitney U test				

Laboratory analysis performed after acute COVID-19 revealed increased D-dimers, fibrinogen, and platelet aggregation in patients treated with CMVHIG compared to patients who did not receive CMVHIG (Table 5).
Laboratory analysis performed after acute COVID-19 revealed increased D-dimers, fibrinogen, and platelet aggregation in patients treated with CMVHIG compared to patients who did not receive CMVHIG (Table 5).

In bivariate logistic regression analysis, diabetes mellitus, the severity of acute COVID-19, and kidney allograft dysfunction during acute infection were identified as significant predictors for CMV reactivation after recovery from SARS-CoV-2 infection (Table 6) however, the number of cases needed to be bigger for multivariate analysis.

Table 6. Bivariate logistic regression analysis for prediction of CMV reactivation after recovery from acute COVID-19. MMF, mycophenolate mofetil; Aza, azathioprin; CMVHIG, hyperimmune antiCMV globulin; IvIG, intravenous immunoglobulin

Bivariate analysis	ß	Wald	OR (95% CI)	P
Therapy (CMVHIG vs. other)	0.51	1.13	1.67(0,64-4.31)	0.29
Diabetes	0.68	3.87	1.98(1.01-3.9)	0.04
Febrility	1.06	4.48	2.89(1.08-7.72)	0.03
Respiratory symptoms	1.35	8.49	3.8(1.56-9.5)	0.004
Pneumonia	1.15	11.5	3.15(1.62-6.09)	<0.001
Other complications during COVID-19	0.80	4.74	2.22(1.08-4.56)	0.03
Allograft dysfunction	0.23	3.91	10.2(1.02-101.5)	0.04
MMF/Aza cessation	0.74	5.25	2.09(1.11-3.94)	0.02
CMVHIG	0.53	1.18	1.69(0.65-4.40)	0.28
IvIg	1.62	5.47	5.06(1.3-19.7)	0.02

ß-regression coeficient

Within six months after acute COVID-19, 40% of patients from the CMVHIG group required hospitalization, compared to 17.3% of patients not treated with CMVHIG (p=0.01). The most common indications in both groups were pneumonia and urinary tract infections.
COVID-19 reinfection was recorded in one patient from the CMVHIG and three patients from the group not treated with CMVHIG.

Discussion

In our retrospective analysis concerning the practice of CMV-HIG off-label use during acute COVID-19, we assessed two main indications: the application of CMV-HIG as adjunctive treatment of acute COVID-19 and CMVHIG as adjunctive treatment of CMV reactivation to the antivirals during the SARS-CoV-2 infection.
Out of 34 patients treated with CMVHIG, two had concomitant SARS-CoV-2 and CMV infection, while others received CMVHIG as adjunctive therapy for COVID-19. Administration of CMVHIG was well tolerated without any side effects. Compared to the rest of our cohort, patients treated with CMVHIG had more severe acute COVID-19, as indicated by the need for mechanical ventilation.
Cytomegalovirus is one of the most significant non-genetic determinants of the immune system with its pronounced immunomodulatory effects. It has the strong potential to shape the course of SARS-CoV-2 infection, either because of CMV reactivation or due to the reshaping of immune response to SARS-CoV-2. However, it remains unclear whether CMV reactivation is a direct consequence of SARS-CoV-2 infection, or results from COVID-19 immunomodulatory therapies [18], but was found to be associated with an increased risk of COVID-19-related hospitalizations [19]. Osawa *et al.* reported that in the population of patients hospitalized in intensive care units, steroid administration, pro-

longed mechanical ventilation, and sepsis have all been recognized as risk factors for CMV reactivation [20].

Prevention and treatment of acute COVID-19 are still not optimal. Vaccination of immunocompromised patients results with frequent breakthrough infections [7], and antivirals are of limited efficacy. Convalescent plasma has been used for treatment of SARS-CoV-2 infection from the beginning of the pandemic with controversial results [21-24]. Convalescent plasma seems to exert its therapeutic potential through direct viral neutralization, antibody-dependent cellular cytotoxicity, complement system activation, and phagocytosis. A cardinal factor in its efficacy is the high level of antibodies administered [25] what was not uniqe and not evaluated in majority of published studies. Dulipsingh *et al*. have shown that subjects with a single infection with SARS-CoV-2 did not have the same levels of neutralizing antibodies that we observed in subjects either in the convalescent or the naive vaccinated groups. Neutralizing antibodies were significantly higher in vaccinated patients than in the convalescent unvaccinated group [26]. As the pandemic evolved, antibody treatment transitioned from convalescent plasma (CP) to monoclonal antibody preparations [27,28]. However, convalescent plasma should still be considered for immunosuppressed COVID-19 patients.

The benefit of IVIG therapy for acute COVID-19 is also controversial [29-31]. As well as with CP, the insufficient effects of IVIG therapy may be the results of dosage, administration timing, and disease severity at the time of administration [32]. Unfortunately, IVIG was usually used for severe or critically ill patients due to the high price and possible side effects. Also, a high number of patients with severe and critical COVID-19 resulted in frequent shortages of IVIG during the pandemic. We used CMVHIG for treatment of CMV infection or for correction of hypogammaglobulinemia in hospitalized patients with moderate to severe acute COVID-19. SARS-CoV-2 infection is often associated with secondary hypogammaglobulinemia, which correlates with the risk of infection and is often treated with immune globulins to support humoral immune responses [33].

In our cohort, patients treated with CMVHIG all had moderate or severe acute COVID-19, and four patients died (11.7%). Reported mortality rates from the literature approaches up to 28% [34-36], suggesting the possible efficacy of CMVHIG as adjunctive therapy for hypogammaglobulinemic immunocompromised kidney transplant recipients and patients with CMV reactivation for treatment of CMV recativation during acute COVID-19.

Data on the use of CMV antivirals in COVID-19 patients is scarce. Interestingly, Schoninger *et al*. failed to find any clear clinical benefit to treating CMV reactivation in the COVID-19 patients in intensive care unit [37]. The ganciclovir-treated subgroup did not display an increased morality rate in Italian study [38]. Our patients responded well to tretament with antivirals and CMVHIG.

While data on tretament of CMV reactivations during acute COVID-19 is limited, even less is known on CMV reactivations post-COVID. In our study, fifty-two patients (12.9%) reactivated CMV infection after recovery from acute SARS-CoV-2 infection. In bivariate logistic regression analysis, diabetes mellitus, the severity of acute COVID-19, and kidney allograft dysfunction during acute infection were identified as significant predictors for CMV reactivation. There was no correlation between the treatment with CMVHIG during acute COVID-19 and CMV reactivation in the post COVID follow up.

Rehospitalizations were frequent. In out previous, multicentre study, the most common indications for hospitalization after acute COVID-19 were pneumonia (24.5%) and renal allograft dysfunction (22.4%), followed by sepsis (14.3%) and thrombotic events (10.2%). The strongest predictor for hospitalization after recovert from SARS-CoV-2 infection in this study was hospitalization for acute COVID-19, while better allograft function decreased the probability of hospitalization [39,40].

During the post-COVID-19 follow up, patients from the CMVHIG group had significantly higher D-dimers, fibrinogen and platelet aggregation. These findings may indicate pro-inflammatory and hypercoagulable state, increasing the likelihood for induction of thromboembolism or stroke [41]. However, only one patient from the CMVHIG group had developed thromboembolic complication (embolization of the ulnarv artery). Reported incidence of IVIG-induced thrombotic complications ranges from 3 to 13% [42]. Risk factors for IVIG-induced thrombosis include male gender, older age, renal insufficiency, diabetes, dyslipidemia, hypertension; immobility; coronary heart disease, history of vascular diseases, family history of thromboembolic diseases, atrial fibrillation, high-dose and high-speed IVIG infusions [43]. In our previous study, the most common laboratory abnormalities after recovery from acute COVID-19 were shortened activated partial thromboplastin time (50%), elevated D-dimers (36.5%), elevated fibrinogen (30.16%), and hypogammaglobulinemia (24%) [39].

Limitations of this study are the retrospective single-centre design, lack of randomization, and the heterogeneity of the available data. The number of patients who received CMVHIG was too small for multivariate analysis. Also, we had no detailed laboratory data during acute COVID-19 for all patients. Additionally, the use of CMVHIG was limited by the length of hospitalization, which was often determined by the pressure of the huge number of infected patients requiring hospital treatment for SARS-CoV-2 infection. However, this is the first study on the use of CMVHIG during acute COVID-19. It indicates a potential benefit of CMVHIG during acute COVID-19 in immunocompro-

mized, hypogammaglobulinemic kidney transplant recipients. Additionaly, based on our experience, it seems that CMVHIG may provide a certain level of antibodies against some other pathogens in the future.

Conclusion

In conclusion, a correction of hypogammaglobulinemia, potential remodeling of the immunological response, and CMV reactivation during acute infection, which adversely affect outcomes in infected individuals, may justify the use of CMV-HIG during acute COVID-19. Its role in protection from SARS-CoV-2 reinfection sholud be investigated. Given the limited therapeutic options and COVID-19 mortality rate, CMVHIG is worth considering. However, prospective randomized trials on the use of CMV-HIG under regimens for dosage, mode, and time of administration are urgently needed to obtain better efficacy and safety data.

Conflict of interest statement. None declared.

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